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Childhood Acute Lymphoblastic Leukemia in the Middle East and Neighboring Countries: A Prospective Multi-Institutional International Collaborative Study (CALLME1) by the Middle East Childhood Cancer Alliance (MECCA)

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Background. Little is known about childhood ALL in the Middle East. This study was undertaken by MECCA as initial efforts in collaborative data collection to provide clinical and demographic information on children with ALL in the Middle East. ***Procedure.*** Clinical and laboratory data for patients with ALL between January 2008 and April 2012 were prospectively collected from institutions in 14 Middle East countries and entered into a custom-built-database during induction phase. All laboratory studies including cytogenetics were done at local institutions. ***Results.*** The 1,171 voluntarily enrolled patients had a mean age of 6.1 ± 3.9 years and 59.2% were boys. T-ALL represented 14.8% and 84.2% had B-precursor ALL. At diagnosis, 5.6% had CNS disease. The distribution of common genetic abnormalities reflected a similar percentage of hyperdiploidy (25.6%), but a lower percentage of *ETV6–RUNX1* translocation (14.7%) compared to large series reported from Western populations. By clinical criteria, 47.1% were low/standard risk, 16.9% were intermediate risk, and 36% were high risk. Most patients received all their care at the same unit (96.9%). Patients had excellent induction response to chemotherapy with an overall complete remission rate of 96%. Induction toxicities were acceptable. ***Conclusions.*** This first collaborative study has established a process for prospective data collection and future multinational collaborative research in the Middle East. Despite the limitations of an incomplete population-based study, it provides the first comprehensive baseline data on clinical characteristics, laboratory evaluation, induction outcome, and toxicity. Further work is planned to uncover possible biologic differences of ALL in the region and to improve diagnosis and management. Pediatr Blood Cancer 2014;61:1403–1410. © 2014 Wiley Periodicals, Inc.

Key words: induction; leukemia; MECCA; pediatric

INTRODUCTION

The population of the Middle East countries is increasing as a result of increased birth rates and growth of the pediatric population. Consequently, the number of children at risk of cancer is increasing rapidly. With the control of infectious diseases and malnutrition, cancer has now assumed a prominent position among the primary causes of morbidity and mortality in children.

Childhood acute lymphoblastic leukemia (ALL), the most common malignancy comprises around 25% of childhood malignancies [1]. Little is known about its clinical and laboratory profile in the Middle East apart from limited single institutional or national studies [2–11]. Additionally, there are few data concerning the types of protocols used in the Middle East, their remission induction rates and induction toxicities.

The Middle East Childhood Cancer Alliance (MECCA) was established in 2000 and is comprised of member institutions in 16 countries in the Middle East and surrounding area. This article reports the results of MECCA's first prospective, multi-institutional, and international prospective collaborative study that provides

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clinical characteristics, laboratory evaluation, induction therapy outcomes, and toxicity of ALL in the Middle East. It was decided that an initial focus of this group should be on the ability to collect high quality clinical, laboratory, and demographic data by limiting this study to the induction phase, given the variability in approaches to subsequent treatment.

The data presented in this article represent the collective experience of the majority of institutions in the Middle East and several surrounding countries involved in the management of ALL (Fig. 1). The aims of the study were to (1) assess feasibility and establish mechanisms for collaborative data collection and management in the Middle East and (2) to collect prospective data on childhood ALL which would serve as background for subsequent clinical studies.

MATERIALS AND METHODS

Study Design

This study was designed as a multicenter descriptive study to collect and analyze prospective data from January 2008 to April 2012 on a variety of parameters. Of the 16 member countries, 14 countries were able to participate (Fig. 1).

Eligibility Criteria

Eligibility criteria included (1) age at diagnosis younger than 18 years of age; (2) the patient being a resident of one of 14 member countries; and (3) having the diagnosis of new onset ALL during the years 2008–2012. Diagnoses had to be confirmed by immunophenotyping at the treating hospitals, except in Yemen, where the diagnosis was based on morphology and histochemistry only.

Data Collection Tools and Methods

A web-based electronic form (SQL format) was designed to collect data. Each country's primary investigator was assigned a country number and protected password. Because ALL treatment is lengthy (2–3 years) and varies with different protocols, it was agreed to limit data collection to the induction phase for this initial study.

The following data were collected using data capture form (DCF) and included: demographic, clinical, laboratory, morphologic, immunophenotypic, and cytogenetic characterization, molecular genetics using fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) methods, response to therapy during and at the end of induction, toxicity profile during induction, and types of protocols/treatment. All collected data were sent electronically to MECCA coordinating office. Quality of data (review of completeness, accuracy, security, and confidentiality of data) was maintained by an assigned research coordinator. All missing fields were verified as truly not available.

Mechanisms for Data Collection

Investigators and research assistants were identified for each country. The procedures for data collection, entry, storage, and data validation were established. A data dictionary and case report form (CRF) were created and a database was developed using Microsoft SQL server (2005) with a web-enabled front end. The database was housed at King Faisal Specialist Hospital and Research Center-MECCA Office, Saudi Arabia and at MECCA Office, Hamad Medical Corporation, Qatar with MECCA as the responsible authority. Remote, password-protected access was provided to each of the countries. Data were extracted from electronic- and paper-based medical records in each country and entered on the CRF. Original CRF hard copies were maintained securely at each treatment center. Data were entered from each participating center under an institutional and patient unique MECCA identifying number. Data verification, validation, and evaluation of accuracy were performed at regular intervals at MECCA Office, Qatar.

Patients and Clinical Data

This study was approved by the authorized clinical research and ethics committees of each center. Informed consents were collected and filed for all patients. Five patient consents were misplaced and those patients were excluded from the study.

Once all data had been entered into the central database, it was audited by one of the Principal Investigators (AA) and the study coordinator/study statistician (PC). Any missing or ambiguous entries were first cross-checked with the CRF copies maintained at MECCA offices and, if not resolved, were discussed at phone or video conference with MECCA investigators for detailed clarification and corrective measures.

Statistical Analyses

Categorical and continuous values were expressed as frequency, percentage, mean, median, standard deviation (SD), and range. Descriptive statistics were used to summarize all demographic, clinical, laboratory, and other characteristics of the patients. Response and outcome during and at the end of induction were studied. Quantitative variables means between the two and more than two independent groups were analyzed using unpaired *t*-test, Mann–Whitney *U*-test, one-way analysis of variance (ANOVA), and Kruskal–Wallis tests. Associations between two or more qualitative variables were assessed using chi-squared test. For small frequencies, chi-squared test with continuity correction factor or Fisher exact test was applied. Pictorial presentations of the key results were made using appropriate statistical graphs. A two-sided P-value <0.05 was considered to be statistically significant. All statistical analyses were done using statistical packages SPSS 19.0 (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

The study was open to all MECCA countries and 14 countries participated. As enrollment was voluntary, not all patients from an individual center representing each of the participating countries were enrolled on this study. Therefore, this was not a full population-based study. The statistical analysis was based on a total of 1,171 enrolled patients. Due to population differences and variable abilities to address the logistical challenges of collaborative clinical research, there were significant differences in the number of patients enrolled; about 75% were submitted by five countries with one contributing 25% of the total number of patients (Fig. 1A).

There were 692 (59.2%) male and 479 (40.8%) females with male to female ratio of 1.4:1 (Table I). The mean age at diagnosis was 6.1 ± 3.9 years (range; 0.2–18 years). The majority of patients 926 (79.4%) were within the 1–10 years of age, 214 (18.4%)

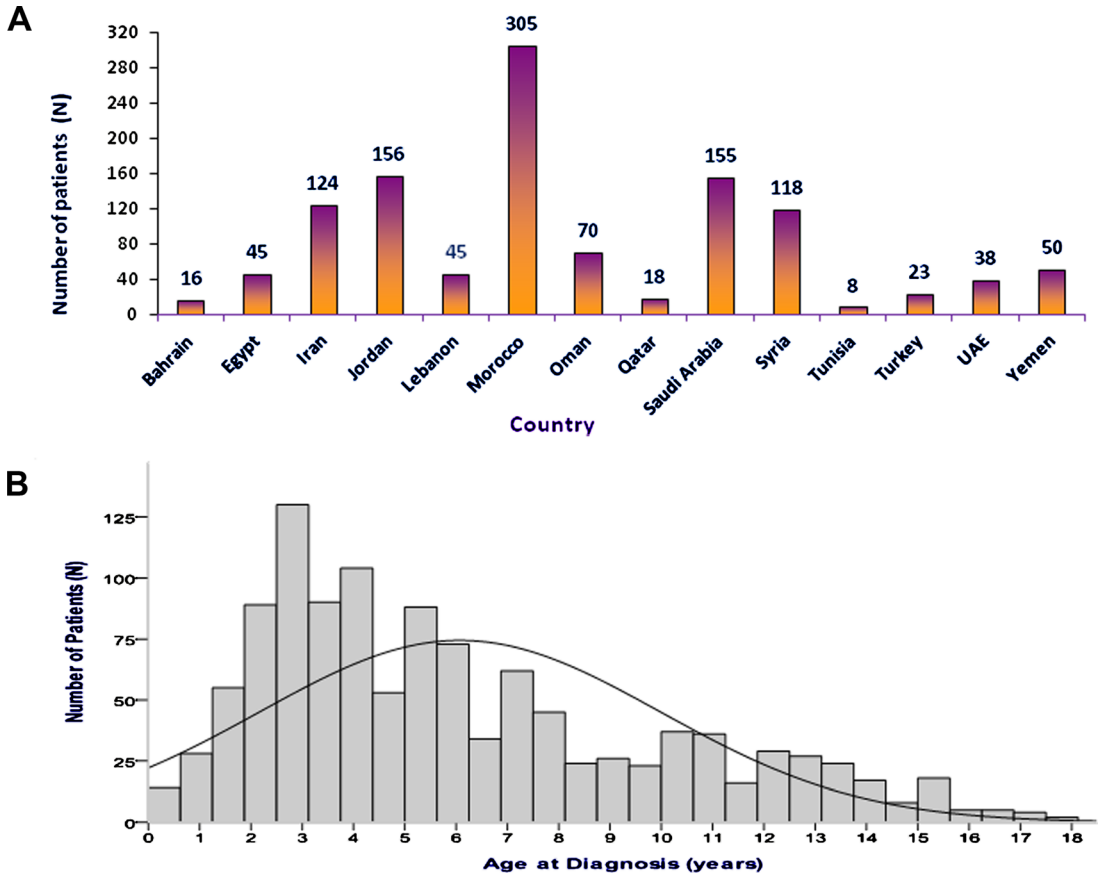

Fig. 1. Number of patients (N = 1,171) and their age at diagnosis. **A**: Number of patients at each country; (**B**) distribution of age at diagnosis.

patients were 10 years or older, and 26 (2.2%) were infants. Peak incidence was observed at 3–6 years of age comprising (33.8%) as shown in Figure 1B.

Of the 1,150 patients reported, 1,114 (96.9%) patients began and continued treatment at the same hospital. Only 36 (3.1%) received care at different hospitals (Table I). Pallor was the most frequent symptom noted in 901 (79.2%) followed by fever in 870 (75.5%) and bone pain in 434 (39.6%). Lymphadenopathy was noted in 712 (62.6%), splenomegaly in 696 (60.8%) and hepatomegaly in 681 (59.5%), testicular involvement was diagnosed clinically in 185 (26.7%) of the patients at diagnosis, but was only proven by biopsy in 17 (2.4%). Other signs and symptoms are shown in Table I.

The median duration of symptoms before diagnosis was 1 month and ranged from 0.1 to 15 months. The majority of patients 900 (87.4%) presented with normal weight to age ratio. Thirty-two (3.1%) patients were labeled as obese with >120% expected weight to age ratio and five (0.5%) patients were ≤50% expected weight to age.

Laboratory Characteristics

The median white blood cell (WBC) count available for 1,159 patients was 12.4×10^9/L, ranged 1 to 715×10^9/L. Only three (0.3%) received steroid therapy prior to referral to the MECCA member cancer center/hospital. The majority of patients 891 (76.9%) had low WBC with only 268 (23.1%) having WBC $\geq 50 \times 10^9$/L. Of these patients, 174 (15%) patients presented with hyperleukocytosis with WBC $\geq 100 \times 10^9$/L. A total of 1,162 patients had a mean hemoglobin 7.9 ± 2.32 g/L and a median platelet count of 36.6×10^9/L (range; 1–614) shown in Table I.

Morphologic (FAB) classification results showed the following: 730 (77.4%) had L1, 192 (20.4%) L2, and 21 (2.2%) L3 of a reported total of 943. Immunophenotyping was available for 1,066 patient samples: 897 (84.2%) had B-lineage, 158 (14.8%) had T cell, and 11 (1%) were classified as mature B cell (Fig. 2). Most of the patients 1,009 (93.3%) did not have central nervous system leukemia (CNS1), while 22 (2%) had CNS3 at diagnosis. An additional 39 (3.6%) had CNS2 status, only 12 (1.1%) patients had traumatic lumbar punctures (TLPs) and their CNS status was decided according to the protocol used (Table I).

Genetic Characteristics

There were significant inter-and intra-country institutional differences in the extent of genetic testing capabilities available. Routine cytogenetic karyotyping was performed on only 496 (42.4%) patients, and this proportion varied greatly between the member institutions. Some institutions were not able to perform conventional cytogenetics. For others, the success rates range varied from 12.5% to 100%. Patients were also tested by FISH and PCR but as with karyotyping, the proportion of patients tested varied significantly. The differences were seen among centers and among the different translocations tested. However, large enough numbers of patients were tested to evaluate the proportional representation of

TABLE I. Demographic, Clinical, Laboratory and Cytogenetic Profiles, Treatment Protocol, Risk Category, Nutritional Status and Induction Outcomes

Characteristics	N	Frequency (%), mean ± SD [median (range)]	Characteristics	N	Frequency (%), mean ± SD [median (range)]
Age at diagnosis (years)	1,171	6.08 ± 3.90 [5.0 (0.2–18)]	Duration of symptoms (months)	1,135	1.35 ± 1.64 [1.0 (0.1–15.0)]
Gender	1,171		Class of case and treatment sites	1,150	
Male		692 (59.2)	Received all treatment in same hospital		1,114 (96.9)
Female		479 (40.8)	Received treatment in different hospitals		36 (3.1)
Sign and symptoms			Translocations (abnormalities)		
Fever		870 (75.5)	t(12;21)(p12;q22)	416	61 (14.7)
Bleeding		281 (25.0)	t(1;19)(q23;p13)	259	16 (6.2)
Pallor		901 (79.2)	t(4;11)(q21;q23)	462	24 (5.2)
Bruising/petechiae		342 (30.8)	t(9;22)(q34;q11)	491	25 (5.1)
Bone pain		434 (39.6)	t(9;11)(p21-22;q23)	99	1 (1.0)
Lymphadenopathy		712 (62.6)	t(11;19)(q23;p13)	89	1 (1.1)
Splenomegaly		696 (60.8)	t(7;9)(q34;q34.32)	77	1 (1.3)
Hepatomegaly		681 (59.5)			
Testicular swelling		185 (26.7)			
Other		178 (17.8)			
CNS status	1,082		Pretreatment laboratory data		
CNS1		1,009 (93.3)	White blood cell (10^9/L)	1,159	54.0 ± 103.8 [12.4 (1–715)]
CNS2		39 (3.6)	WBC $< 50 \times 10^9$/L		891 (76.9)
CNS3		22 (2.0)	WBC $\geq 50 \times 10^9$/L		268 (23.1)
TLP		12 (1.1)	Hemoglobulin (g/L)	1,162	7.9 ± 2.3 [7.9 (2–15.7)]
			Platelets (10^9/L)	1,162	66.1 ± 81.1 [36.6 (1–614)]
Morphology	943		Risk category by reporting	1,101	
L1		730 (77.4)	Standard risk (SR)		519 (47.1)
L2		192 (20.4)	Intermediate risk (IR)		186 (16.9)
L3		21 (2.2)	High risk (HR)		396 (36.0)
Immunophenotype	1,066		B lineage risk category NCI/Rome	894	
Precursor B		897 (84.2)	Standard risk (SR)		622 (69.6)
T-cell		158 (14.8)	High risk (HR)		272 (30.4)
Mature B		11 (0.9)			
DNA index (precursor B)	242				
<1.16		135 (55.8)	Testicular leukemic		17 (2.4)
≥1.16–1.60		101 (41.7)			
>1.60		6 (2.5)			
Cytogenetics performed			Nutritional status	1,030	
Yes		496 (42.4)	Normal 120–80% weight/age		900 (87.4)
No		675 (57.6)	Obese >120% expected weight/age		32 (3.1)
			Grade I–IV <50–79% weight/age		98 (9.5)
Results of cytogenetics	433		Treatment protocol	1,171	
Normal		284 (65.6)	CCG		128 (10.9)
Abnormal		149 (34.4)	BFM		351 (30.0)
			SJCRH		111 (9.5)
			UK		65 (5.5)
			Modified international or local		516 (44.1)
End of Induction outcomes	1,042		CBC at end of induction		
M1			WBC (10^9/L)	1,051	4.9 ± 3.1 [4.2 (0.2–36.4)]
M2		1,007 (96.6)	Hemoglobin (g/L)	1,055	10.2 ± 1.6 [10.1 (2–16.6)]
M3		21 (2.1)	Platelets (10^9/L)	1,052	295.3 ± 170.7 [271 (7–996)]
		14 (1.3)	ANC (%)	1,012	38.8 ± 19.9 [40 (0–90)]
			Blast (%)	996	0.4 ± 4.1 [0 (0–80)]

CNS, central nervous system; TLP, traumatic lumbar puncture; ANC, absolute neutrophil counts; M1, complete remission; M2, incomplete remission; M3, refractory disease; CCG, Children's Cancer Group; BFM, Berlin-Frankfurt-Munster; SJCRH, St. Jude Children's Research Hospital; UK, United Kingdom; NCI, National Cancer Institute.

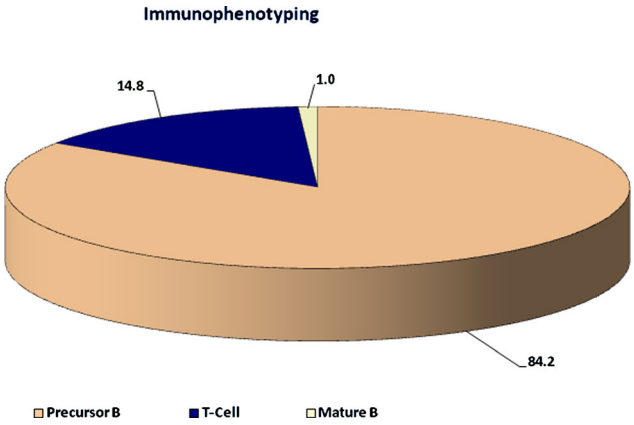

Fig. 2. Institutional classification of ALL types.

these cytogenetic abnormalities. When calculating the proportion positivity in the cohort, the denominator used varied by test and depended on the ability of the particular test(s) to identify the abnormality. Except *ETV6–RUNX1* translocation, which is not detectable by routine karyotyping, all translocation frequencies were assessed using the three modalities of conventional cytogenetics, FISH, and PCR.

ETV6–RUNX1 translocation was detected in 61 (14.7%) of precursor B cell from the leukemia samples of 416 patients, followed by *TCF3–PBX1* in 16 (6.2%) of 259 tested. *MLL* gene rearrangements were observed in 24 (5.2%) of 462 patients tested and *BCR–ABL1* demonstrated in 25 (5.1%) from 491 patients tested. These and other translocations are shown in Table I.

Numerical chromosomal abnormalities were detectable by karyotyping as well as by determination of the DNA index by flow cytometry. Both of these methods were considered when determining the cellular ploidy of leukemic blasts. DNA index was not performed at many participating countries. It was done on only 242 out of 897 (27%) of Precursor B ALL samples: DNA index of <1.16 in 135 (55.8%), ≥ 1.16–1.6 in 101 (41.7%), and >1.60 in 6 (2.5%) (Table I). Cytogenetic data showed 119 (25.6%) had ALL that was hyperdiploid out of a total number of 465 patients reported, 58 (15%) out of 387 patients reported having trisomies and 152 (30.6%) out of 496 patients reported having a diploid chromosome number. Clear data were not available for other cytogenetic abnormalities. Because testing for trisomies 4, 10, 17 was done in a very small minority of patients, these results are not shown.

Treatment Protocol and Risk Categories

Multiple protocols were used as shown in Table I. Most of the patients were treated on international protocols 655 (55.9%) and 516 (44.1%) on modified international or local protocols. By

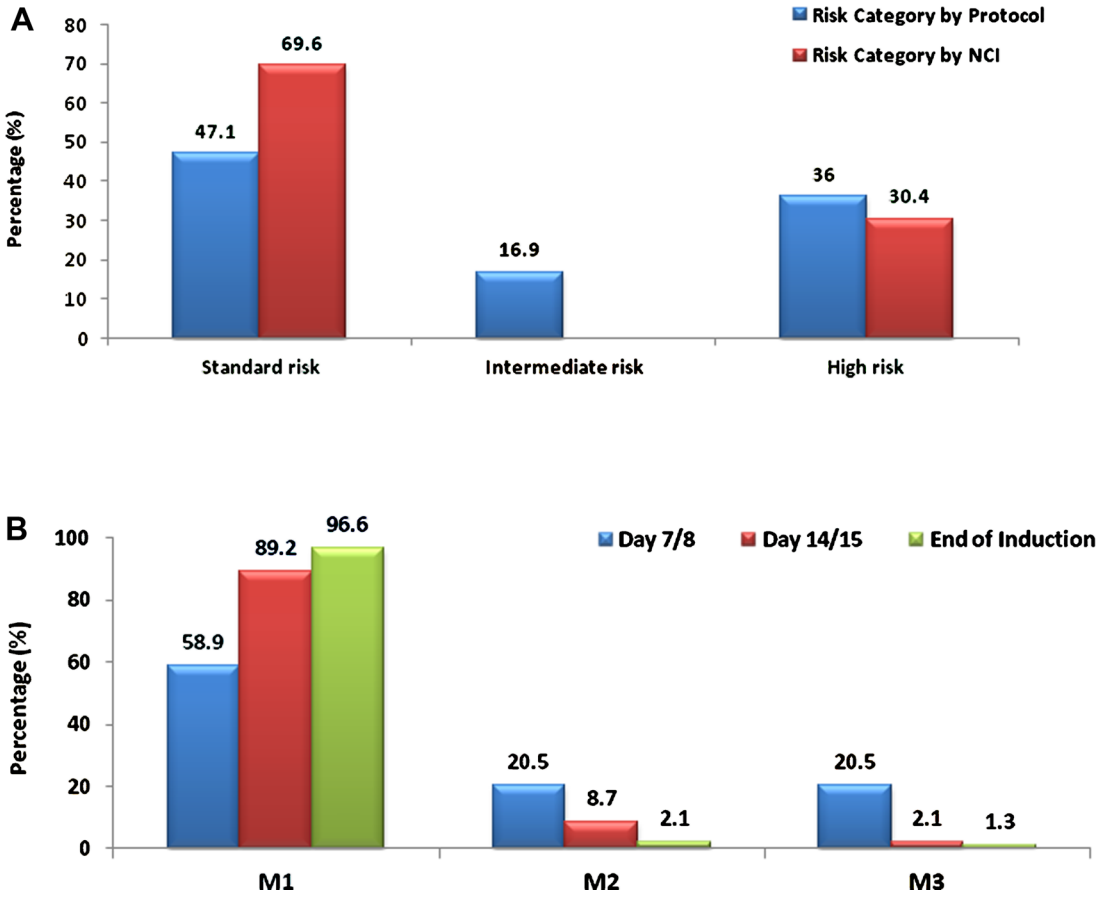

Fig. 3. **A**: Risk category; (**B**) response to induction therapy.

clinical criteria, 519 (47.1%) of the patients were assigned to the low/standard-risk category, 186 (16.9%) to the intermediate, and 396 (36%) to the high-risk category. However, when we analyzed risk category assignment using NCI/Rome criteria for precursor B ALL, 622 (69.6%) were standard-risk and 272 (30.4%) were high-risk group (Fig. 3A).

Response to Induction Therapy

Day 8 peripheral blood blasts count for 97 patients treated on BFM protocol with available data showed 88 (90.7%) as good steroid responders and 9 (9.3%) as poor steroid responders. Day 7 BM showed M1 in 66 (58.9%) and 23 (20.5%) as M2 or M3 bone marrow, respectively, out of a total of 112 patients tested. By Day 15, of 619 patients reported, 552 (89.2%) had M1 bone marrow, and 54 (8.7%) had M2 and 13 (2.1%) had M3 bone marrow. By the end of induction, of 1,042 patients reported, 1,007 (96.6%) were in complete remission. Twenty-one patients (2.1%) had M2 marrows and 14 (1.3%) had disease refractory to therapy as defined by M3 marrow status (Table I and Fig. 3B). Various prognostic factors such as age, gender, WBC, cell lineage, risk category by NCI/Rome, CNS status, immunophenotype, DNA index, genotype, and protocol showed no significant association with end of induction response ($P > 0.005$; Table II).

Complications

Tumor lysis. Prior to treatment, 249 patients (26%) of 975 had elevated uric acid level, 148 (18.0%) of 820 patients had elevated phosphorus, and 27 patients (2.5%) of 1,069 elevated potassium. By reporting, 10.1% of the patients had tumor lysis syndrome.

Bleeding. On presentation, 281 (25%) of the patients had bleeding and, during induction 179 (15.3%) had bleeding and received blood products.

Toxicities

Fever and neutropenia. Forty-eight percent of the 564 patients experienced fever and neutropenia during induction. Eleven percent (11.4%) had documented infections, 91 (7.8%) had bacterial sepsis, 35 (3%) had gram positive, 56 (4.8%) had gram-negative sepsis, and 29 (2.5%) patients had shock with infection and 10 (0.9%) patients had fungal infection.

Other Toxicities

Oral mucositis was observed in 249 (21.3%), diarrhea in 139 (11.9%), arrhythmias in 5 (0.4%), heart failure in 2 (0.2%), avascular necrosis of the hip in 6 (0.5%), seizure in 10 (0.9%), motor neuropathy in 9 (0.8%), and sensory neuropathy in 8 (0.7%) (Table III).

TABLE II. Association of Different Prognostic Variables With End of Induction Outcomes

	N	Complete remission	Incomplete remission	*P*-value
Age at diagnosis (years)	1,042			
<1		20 (95.0)	1 (5.0)	0.752
1–10		798 (96.8)	26 (3.2)	
≥10		189 (95.9)	8 (4.1)	
Gender	1,042			
Male		597 (96.8)	20 (3.2)	0.800
Female		410 (96.5)	15 (3.5)	
White blood cell (10^9/L)	1,038			
<50		773 (96.5)	28 (3.5)	0.685
≥50		230 (97.0)	7 (3.0)	
Risk category by reporting	992			
Standard risk (SR)		435 (97.3)	12 (2.7)	0.026
Intermediate risk (IR)		177 (98.9)	2 (1.1)	
High risk (HR)		347 (94.8)	19 (15.2)	
B lineage risk category by NCI/Rome	804			
Standard risk (SR)		542 (97.7)	13 (2.3)	0.307
High risk (HR)		240 (96.4)	9 (3.6)	
CNS status	985			
CNS1		898 (96.8)	30 (3.2)	0.261
CNS2		34 (91.9)	3 (8.1)	
CNS3		19 (95.0)	1 (5.0)	
Immunophenotype	944			
Precursor B		784 (97.3)	22 (2.7)	0.911
T-cell		134 (97.1)	4 (2.9)	
Testicular leukemic	692			
Yes		17 (100)	0 (0)	0.407
No		646 (96.1)	29 (3.9)	
DNA index (precursor B)	235			
<1.16		127 (97.7)	3 (2.3)	0.546
≥1.16–1.60		97 (98.0)	2 (2.0)	
>1.60		6 (100)	0 (0)	

CNS, central nervous system; NCI, National Cancer Institute.

TABLE III. Toxicities Reported During Remission Induction Therapy

Toxicities	N	Percentage
Tumor lysis	118	10.1
Bleeding	179	15.3
Fever and neutropenia	564	48.2
Positive blood cultures	111	8.5
Bacteria	91	7.8
G positive	35	3.0
G Negative	56	4.8
Fungus	10	0.9
Urticaria	34	2.9
Anaphylaxis	4	0.3
Bronchospasm	14	1.2
Cardiac		
Arrythmia	5	0.4
Heart failure	2	0.2
Gastrointestinal		
Oral mucositis	249	21.3
Gastritis	111	9.5
Pancreatitis	8	0.7
Typhlitis	23	2.0
Diarrhea	139	11.9
Constipation	65	5.6
Musculoskeletal		
Osteonecrosis	6	0.5
Osteoporosis	4	0.3
Neurotoxicity		
Sensory neuropathy	8	0.7
Motor neuropathy	9	0.8
Paralysis	5	0.4
Seizure	10	0.9
Ataxia	3	0.3
Thrombotic events		
Associated with central venous catheter	2	0.2
Not associated with central venous catheter	5	0.4

Co-morbidities: Fourteen patients had congenital chromosome disorders most commonly trisomy 21 Down syndrome, 13 patients had blood disorders, 2 patient immune deficiencies, 2 patients prior malignancy, and 1 patient had prior myelodysplastic syndrome.

Mortality. Of the total 1,171, 1,042 (89%) had their end of induction bone marrow reported. Of the remaining 129 (11%) patients, who did not have their end of induction bone marrow reported, 62 (48.1%) had missing data from one country (Syria). There were less than 2% deaths in the entire cohort.

DISCUSSION

The clinical features and outcome results of childhood cancer in the Middle East are largely unknown. This study is a first step towards a better understanding of ALL, the most common childhood malignancy, in the Middle East. We report the results on 1,171 children. The study also represents the first large, collaborative undertaking by institutions in the Middle East and surrounding countries. However, this study does not include all countries in the Middle East as some opted not to participate and others could not submit the required data. Similarly, not all centers in those countries who elected to participate were included in this study. Efforts are needed to improve national and institutional participation as well as accrual rates and quality of data submitted. In spite of these limitations, this study demonstrates the willingness and ability of investigators in the Middle East to create a functional cooperative group.

The peak age range of 3–6 years is similar to the childhood ALL reported from the west. Gender ratio of M/F (1.4:1) may be slightly higher than reported gender ratio from the west. Among the signs and symptoms, presentation with bone pain (39.6%) appears higher than reported in the west and closer to Hong Kong report [12]. Although testicular involvement was suspected clinically in 185 (26.7%), only 17 (2.4%) had the confirmed diagnosis of testicular leukemia. The high percentage of patients with suspected but not confirmed testicular involvement reflects limited accuracy of testicular involvement evaluation by clinical examination as opposed to other diagnostic modalities such as biopsy. The majority of patients 87.4% had normal nutritional status and only 3.1% were obese. The overwhelming majority of patients (96.9%) received care at their local or regional hospitals. Only 3% had to be transferred to other hospitals. The duration of symptoms before evaluation at the hospital was short with a median of 1 month and a mean of 1.35 ± 1.64 months; this appears comparable to delay time reported from developed countries and much shorter than the previous expectation which reflects improvement in public health education, access to care and diagnostic facilities. It is also notable that out of the total of 1,171 patients, only 12 patients (1.1%) had TLP.

The French American British (FAB) classification of ALL showed 77.4% L1, 20.4% L2, 2.2% L3 which is in keeping with international data. T cell immunophenotype of 14.8% is also within the percentage reported from the west, but possibly lower than reported series in developing countries. This may reflect race and ethnicity, geography, socio-economics status, environmental factors, and access to care [13–15].

There was no increase in the number of patients with higher risk genetic lesions such as *BCR–ABL1*, *MLL* gene rearrangement and *TCF3–PBX*. While the percentage of the hyperdiploidy (25.6%) was similar to that reported in the west, the percentage of the other favorable genetic marker *ETV6–RUNX1* (14.7%) appeared lower than reported in the west. Whether these lower incidence rate related to variability in technical capacities of detecting these genetic change will be subject of future MECCA studies.

The 14.7% of *ETV6–RUNX1* appears lower than the 20% incidence reported from United States and Europe but may be closer to the rate reported from South Asia and some other developing countries [16–22]. The lower proportion of "good risk" ALL has been implicated as a contributing cause to the overall worse outcome of patients. However, among Middle East countries and other developing countries some have reported a 20% result similar to USA and Europe [3]. Our 411 patients were tested by FISH and PCR, but whether the lower representation is due to real difference or technical issue will await next MECCA translational research study. One future potential solution may be the establishment of a MECCA referral laboratory which is capable of performing advanced molecular studies. Such a laboratory would serve all MECCA institutional members treating ALL. Data on cytogenetic abnormalities were limited and were clearly reported on only 56% of the patients who had cytogenetics tested. The distribution of hyperdiploidy which is reported as 25.6% is similar to the 20–25%

reported from the west. Cytogenetic testing was done on 42.4% of patients, which likely reflects the lack of well-established cytogenetics laboratories in most of the Middle East countries. Improvements are needed in the set up and standardize such testing in the Middle East.

There are multiple different protocols used in the Middle East and MECCA is trying to unify the diagnostic approach as well as treatment protocols. By clinical and NCI/Rome criteria of risk stratification, the percentage of high-risk patients which is about a third of the patients is comparable to the percentage in the west.

Early steroid response, for patients treated on BFM protocol, as assessed by Day 8 peripheral blood blast count (90.7% prednisone good response) is compatible with reported literature from the west. End of induction remission rate (96.6%) and toxicities profile reflect that the induction regimens used were effective and had tolerable toxicities. Minimal residual disease (MRD) was not available except at very few centers and therefore was not reported. It is hoped that in the future central MECCA lab will perform such tests. In addition, a comparative analysis of ALL in the different countries as well as the comparative analysis of B-lineage and T cell ALL will be the subject of subsequent publications.

In conclusion, we believe that this study provides proof of principle that collaborative clinical research with a centralized data repository is feasible in the Middle East. The data derived from this study have begun to demonstrate the clinical profile and disease characteristics of ALL in the Middle East. We have identified areas of needed improvement both in terms of diagnosis, risk classification, and assessment of response. This effort is anticipated to lead to standardization of diagnosis and adoption of a uniform protocol for MECCA countries. MECCA efforts can lead to treatment strategies and outcome, reduced morbidity and mortality and better quality of life for children with cancer similar to the successful efforts of the collaborative groups in North America and Europe.

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